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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,892	08/18/2006	Shinobu Akuzawa	03327.2355	2819

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
ORWIG, KEVIN S	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,892	AKUZAWA ET AL.	
	Examiner	Art Unit	
	Kevin S. Orwig	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9 and 11-18* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/18/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/25/09, 1/20/10, 3/19/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 9 and 12-18 are currently pending and are the subject of this Office Action. This is the first Office Action on the merits of the claims. Claim 11 is withdrawn.

Election/Restrictions

Applicants' election of Group IV (claim 9) in the reply filed on Dec. 7, 2009 is acknowledged. Applicant has elected Group IV without traverse.

In the response of Mar. 18, 2010, applicants elected the following species:

Structure of the selective dual antagonist:

Single Cmpd: N-(diaminomethylene)-9-hydroxy-9H-fluorene-2-carboxamide

Separate Cmpds: 2-amino-4-(4-fluoronaphtho-1-yl)-6-isopropylpyrimidine (i.e. **RS-127445**)

((R)-3-(2-(4-methylpiperidine-1-yl)ethyl)pyrrolidine-1-sulfonyl)phenol (i.e. **SB-269970**)

In a telephone call on 6/15/10, applicants' elected the embodiment wherein a single compound having dual activity is used (i.e. claim 12). Thus, claim 11, which recites the administration of two separate compounds, is withdrawn as being directed to a non-elected species. A search of applicants' elected species for the single compound N-(diaminomethylene)-9-hydroxy-9H-fluorene-2-carboxamide indicated that this compound was free of the prior art.

Information Disclosure Statement

The references provided on the information disclosure statement(s) were considered and have been made of record to the extent that each was provided. References lined-through on the information disclosure statement(s) were not considered because they were not provided or were not provided in English.

Specification

The specification is objected to because the claim for domestic priority to PCT/JP2005/002946 has not properly been made.

It is noted that this application appears to claim subject matter disclosed in prior Application No. PCT/JP2005/002946, filed 2/17/05. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date

on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference

in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 9 and 11-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the claims encompass *any* dual antagonist for the 5-HT_{2B} and 5-HT_7 receptor (i.e. both single compounds having dual activity and separate compounds administered together), but applicants were clearly not in possession of any and all such compounds at the time of filing.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical

invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office (PTO) Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. at 1106). Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP §2163. However, if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP §2163.

The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Univ. of Rochester v. G.D. Searle*, 69 USPQ2d 1886, 1892 (CAFC 2004). A description of what a material does, rather than of what it is, usually does not suffice to provide an adequate written description of the invention. *Univ. of Cal. V. Eli Lilly*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Furthermore, to the extent that a functional description can meet the requirement for an

adequate written description, it can do so only in accordance with PTO guidelines stating that the requirement can be met by disclosing "sufficiently detailed, relevant identifying characteristics," including "functional characteristics when coupled with a known or disclosed correlation between function and structure." *Univ. of Rochester v. G.D. Searle*, 69 USPQ2d 1427, 1432 (DC WNY 2003).

In paragraph [0044] of the published application, applicants disclose a genus of compounds (related by the core fluorine structure) that are asserted to have the claimed dual 5-HT_7/5-HT_{2B} antagonism properties. Only 8 compounds are actually disclosed as having the claimed receptor binding profile (see par. [0148]). Moreover, the claims are in no way limited to this genus of compounds. Applicants have failed to provide sufficient description of the various compounds as recited in instant claim 9 that would provide adequate written description of the compounds encompassed by the scope of the claim. Adequate written description requires a precise definition, such as by structure, formula, and chemical name, in combination with physical properties. In the present case, other than the specific derivatives mentioned (see pars. [0044] and [0148]), the disclosure fails to describe the claimed compounds in a manner that complies with the written description requirement of 35 U.S.C. 112, 1st Paragraph.

Claim Rejections - 35 USC § 112 (1st Paragraph)

Scope of Enablement

Claims 9 and 12-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Claims 9 and 12-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment or inhibition of migraines, does not reasonably provide enablement for prophylaxis or prevention of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Specifically, the method of *prophylaxis of migraine* has not been sufficiently taught to enable the full scope of the claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the scope or breadth of the claims;

3) the state of the prior art;

4) the predictability or unpredictability of the art;

5) the relative skill of those skilled in the art;

6) the presence or absence of working examples;

7) the amount of direction or guidance presented and,

8) the quantity of experimentation necessary.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Scope or breadth of the claims: Instant claim 9 recites a method for prophylaxis of migraine. Stedman's Medical Dictionary defines prophylaxis as: "Prevention of disease or of a process that can lead to disease. [Mod. L. fr. G. *pro-phylasso,*1 to guard before, take precaution]". Thus, the term prophylaxis reasonably encompasses prevention, in light of the specification. See pars. [0003], [0006], and Example 1, pars. [0151] and [0159]. However, the instant specification as originally filed lacks adequate guidance, direction or discussion to apprise the skilled artisan of how to prevent migraines. The claims are broad in that they claim a method for *preventing* migraines, the breadth of which exacerbates the complexity of the invention. The term "preventing" is a potent and absolute term indicating that the method of prevention will necessarily prevent the onset of any migraine, regardless of the cause, and in every instance by the administration of the claimed antagonist. Since the instant specification provides no limiting definition of the term "prophylaxis", the term has been interpreted expansively, and encompasses preventing as discussed above. The term "preventing" encompasses a wide range of situations, from preventing a disease from occurring to preventing it from progressing. Nor is the term limited by any time frame.

Applicant is claiming a method for prophylaxis (i.e prevention) in claims 9 and 12-18. Prevention, as defined by Merriam-Webster Dictionary, is to keep from happening or existing, which implies taking advance measures against something possible or probable. Furthermore, the act of preventing embraces complete 100% inhibition. Thus, the burden of enablement in the assertion of this claim is much higher than would be the case of enabling simply the treatment of the condition. As for the instant

application in relation to the prior art, neither the prior art nor the instant application enable for prevention of migraines. Nowhere in the instant application has the efficacy of the elected composition been enabled to prevent the occurrence of ischemic related conditions. Since absolute success in preventing most diseases/conditions is not reasonably possible, the specification, which lacks an objective showing that ischemic related conditions can actually be prevented, is viewed as lacking an adequate written description of the same.

The claim is thus extremely broad insofar as it suggests that following administration of the claimed composition, one will not experience migraines again; that should one already have a migraine, it will not worsen; and that it will not recur again for the life of the subject from the time of the application forward. While such "prevention" might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the "real world" in which patients live.

State of the prior art: Pharmaceutical (and other) treatments for migraines are well known. However, the state of the art with regard to preventing migraines is essentially non-existent. Examples of migraine prevention have not been described in the art.

Relative skill possessed by those in the art: In view of the discussion of the state and predictability of the prior art, and the scope of the claims, which are drawn to a method of preventing migraines, the level of skill in the art is high and is at least that of a medical doctor or Ph.D. scientist with several years of experience in the field(s) of pain management, specifically migraine diagnosis and management.

Presence or absence of working examples: No working examples of preventing migraines were provided.

Amount of guidance or direction provided: In considering the guidance provided in the specification, only Example 1 deals with the method of preventing migraines. But example 1 is only concerned with an *in vivo* protein leakage assay that is asserted to be related to the onset of migraine (not the prevention thereof). Even the data presented in this example state that the tested compounds almost completely suppressed the amount of leaked protein. But even if, *in arguendo*, these data were shown to be properly correlated to the onset of all migraines (which they have not been), this assay says nothing about the effect on future occurrences of migraines. The full scope of the claims is not supported by these data. No guidance or evidence is presented as to how one can actually prevent migraines.

Quantity of experimentation required to make and use the invention: In view of the factors discussed above, the state of the art with regard to preventing migraines in general is fairly complex and sufficiently unpredictable such that the skilled artisan would have been required to undertake undue experimentation to determine the exact conditions and manner and/or process of execution to arrive at those conditions amenable to actually preventing migraines in the absence of detailed guidance to this effect. Absent such direction or guidance as to how the skilled artisan would go about preventing migraines, one of ordinary skill in the art would have no alternative recourse but to undertake an exhaustive, and, thus, unduly burdensome search of methods to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9 and 12-18 are rejected under 35 U.S.C. 102(b) as being anticipated by CRAIG (U.S. 6,440,988; Issued Aug. 27, 2002).

1. Craig discloses a method of treating a subject comprising administering a therapeutically effective amount of an antagonist that binds to both 5-HT_7 and 5-HT_{2B} receptors (abstract; col. 4, lines 40-41). Craig teaches that the 5-HT_7/5-HT_{2B} antagonist binds the 5-HT_7 receptor and the 5-HT_{2B} receptor with an affinity at least 10-fold higher than the affinity with which it binds each of the human α_1($_{1A}$ or $_{1B}$) adrenoceptor, dopamine D_2 receptor, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, and 5-HT_6 receptors (col. 4, lines 50-56; col. 8, lines 10-14 and 36-46). Thus, Craig teaches the only active step of the instantly claimed method (i.e. claim 9), and teaches a pharmacokinetic profile that matches that claimed exactly except for being silent as to the affinity of the compounds at the M_1 (muscarinic) receptor. Nonetheless, given that the antagonists fit the instantly claimed profile at every other receptor claimed, it is highly likely that these compounds inherently have a higher binding affinity at the 5-HT_7 and 5-HT_{2B} receptors than at the M_1 receptor as well. Moreover, the instant claims encompass receptors from any species of animal (i.e. not just human). Thus, in

absence of evidence to the contrary, the compounds disclosed by Craig inherently have a higher binding affinity at the 5-HT_7 and 5-HT_{2B} than at least one other M_1 receptor from a non-human animal. Craig reads on claims 9 and 12-18.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Patent Application No. 11/997,956

Claims 9 and 12-18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 22 of copending Application No. 11/997,956. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the '956 claims anticipates or renders obvious that of the instant claims. The difference between the two claim sets is that the '956 claims do not recite the receptor binding affinities instantly recited. However, as stated above, the receptor binding affinities are merely an inherent property of the compounds recited in the '956 claims, which encompass the compounds described in the instant application to have these attributes along with many compounds that are no more than close structural analogues thereof, and would

therefore be expected to have the same properties. Thus, the entire scope of the instant claims is anticipated or rendered obvious by the '956 claims.

Conclusion

Claims 9 and 12-18 are rejected. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin S. Orwig whose telephone number is (571)270-5869. The examiner can normally be reached Monday-Friday 7:00 am-4:00 pm (with alternate Fridays off). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached Monday-Friday 8:00 am-5:00 pm at (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin S Orwig/

/Sharmila Gollamudi Landau/
Supervisory Patent Examiner, Art Unit 1611